Letters

Is the loss of cerebral cortical choline acetyl transferase activity in Alzheimer's disease due to degeneration of ascending cholinergic nerve cells?

Sir: Although some of the marker enzyme choline acetyl transferase may be present in cholinergic neurons intrinsic to the cerebral cortex,¹ most is thought to reside within the terminals of ascending fibres whose nerve cell bodies are located within that area of brain known as the substantia innominata.^{1,2} Reductions in cerebral cortical choline acetyl transferase activity in Alzheimer's disease³⁻⁶ may therefore reflect dysfunction of these nerve cells. Alterations in the capacity to form proteins needed for physiological function are indicated⁷ by changes in nerve cell nucleolar volume and cytoplasmic RNA content.

We have measured⁸ these features in 60 nerve cells of the substantia innominata, in each of 12 demented patients dying with histologically verified Alzheimer's disease (mean age 81.2 ± 1.3 yrs; necropsy delay 32.9 ± 2.8 h) and in eight others (mean age 78.2 ± 1.7 yrs; necropsy delay 36.7 ± 3.1 h) with multi-infarct dementia. Findings are compared with those from a control group of eight patients (mean age 80.4 ± 1.3 yrs; necropsy delay 32.4 ± 4.0 h) dying without neurological or psychiatric disease and judged to be mentally preserved.

When compared with controls both nucleolar volume and cytoplasmic RNA content were significantly reduced in Alzheimer's disease by 34 and 32% respectively, whereas neither was altered in multi-infarct dementia (Table). Such changes in function in Alzheimer's disease are consistent with other findings⁹⁻¹¹ of neuronal degeneration and loss of choline acetyl transferase activity in this region of the brain, and indicate that the loss of cerebral cortical choline acetyl transferase activity in Alzheimer's disease,³⁻⁶ is probably mainly due to reduced levels of function within the perikarya of cholinergic neurons of the substantia innominata. The smaller decreases in cortical choline acetyl transferase activity reported in multi-infarct dementia^{3,4} most likely stem from tissue destruction caused by local circulatory deficits or the involvement of cholinergic synapses in the few senile pla-

Table

Group	Nucleolar volume (μm^3)	Cytoplasmic RNA content (Arbitrary units)
Control (n = 8)	31.6 ± 2.3	34.7 ± 1.6
Alzheimer's disease (n = 12)	$20.8 \pm 1.9^*$	$23.6 \pm 1.2^*$
Multi-infarct dementia (n = 8)	32.4 ± 2.5	35.8 ± 1.9

Values are means $\pm$ SEM

*p < 0.001, compared with control values

ques usually present in these patients.

The degeneration in Alzheimer's disease, but not in multi-infarct dementia, of other nerve cells which also give rise to ascending pathways, such as those of the locus caeruleus,¹²⁻¹⁵ vagus nerve nucleus,¹⁵ and hypothalamus,¹⁶ suggests that the cholinergic changes, in Alzheimer's disease, may be only one facet of a wider process of deprivation of cerebral input and may partly explain why the many therapeutic trials aimed at restitution of the cholinergic system alone, have, so far, met with little success.

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Insulin-induced hypoglycaemia does not abolish chorea

Sir: Pathological changes occur in the hypothalamus in Huntington's disease.¹ Insulin tolerance tests have been used to examine hypothalamic function in such patients, and mild abnormalities of growth hormone secretion have been described.²⁻⁴ In the course of such an investigation, Keogh *et al*² noted that chorea ceased some 30 min after the insulin injection and was not evident for the next 60 to 75 min in all of the twelve patients studied. They did not think that this dramatic change was due to

an altered level of consciousness, for "all patients were awake throughout the investigations and were checked repeatedly to see that they were capable of verbal communication". Subsequently, Lavin *et al*³ described similar observations in another group of eight patients with Huntington's disease, in all of whom chorea disappeared for at least an hour within about half-an-hour of the insulin injection. Such a dramatic effect on chorea might provide some clue as to the pathophysiology of that movement disorder, so we have repeated the study concentrating on the effect of insulin-induced hypoglycaemia on the chorea.

Five patients with Huntington's disease (four males and one female; aged 30 to 70 years; with disease duration from 2 to 13 years; four on no drugs and one on tetrabenazine 25 mg three times daily) with obvious chorea were studied. After an overnight fast, blood was withdrawn for glucose estimation, and insulin (0.1 mg/kg) was injected into the opposite arm. Blood sugar and clinical response were measured every 10 min for 60 min, and then every 20 min for a further 60 min. The severity of chorea was rated using a specially designed scale described in detail elsewhere.⁵ In addition the number of choreic movements occurring at rest in one selected region, such as an eye, finger or toe depending on the individual patient, was counted over a 60 sec period. Blood sugar fell below 2.0 mmol/l and symptoms and/or signs of hypoglycaemia developed in all subjects. However, the intensity of chorea did not alter. Three subjects fell asleep during the test, and chorea disappeared in two, but on arousal their chorea was of the same severity as before insulin. Unfortunately, insulin-induced hypoglycaemia had no effect on chorea in our patients.

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Periodic alternating nystagmus in a case of hereditary ataxia and its treatment with baclofen

Sir: I describe below a patient with a dominantly inherited cerebellar degeneration who presented with oscillopsia, and was found to have periodic alternating nystagmus. His symptoms were virtually abolished following treatment with baclofen, which confirms a recent finding in two out of three cases of periodic alternating nystagmus similarly treated.¹ Periodic alternating nystagmus itself is a rare and extraordinary form of spontaneous nystagmus. It is a horizontal, usually jerk nystagmus which changes direction periodically. Less than a hundred cases are to be found in the literature in association with a considerable variety of disorders including multiple sclerosis, posterior fossa malformations and tumours, phenytoin intoxication and neurosyphilis. One previous case has been reported in a hereditary ataxia (Friedreich's ataxia),² but the veracity of the diagnosis in that case has been questioned.³

A 34-year-old salesman presented with a four year history of increasingly troublesome oscillopsia. His father and grandfather had both developed ataxia in middle life. The former is living, has been investigated elsewhere, and a diagnosis of hereditary ataxia made; he has nystagmus, but details are not known. No other family members are as yet affected. On examination cavoid feet and alternating nystagmus were noted, but no other abnormalities. Routine blood count and biochemistry were normal. Acanthocytes were looked for but none seen. Serological tests for syphilis were negative. Skull radiographs were normal but a CT scan showed marked brain stem and cerebellar atrophy. Nerve conduction studies and visual evoked responses were within normal limits. The upper trace in the figure is a continuous record of the patient's periodic alternating nystagmus with eyes in the primary position. The cycle length is 182 seconds with a left beating phase of 80 seconds, a right beating phase of 76 seconds and two null phases of 12 and 14 seconds respectively.

The second trace shows a series of saccades 30° to either side of the primary position, recorded at a lower gain. At the start of the trace the null position is at 30° left, as it shifts to the primary position first degree nystagmus to the left appears and increases in amplitude. It has been commented previously that the nystagmus can be conceptualised as resulting from periodic shifts of the null zone.⁴ Other features were also similar to most previously reported cases (for example the three analysed in detail by Baloh *et al*).⁵ The spontaneous nystagmus was superimposed on saccades and smooth pursuit. Optokinetic nystagmus could be produced only during null phase or when the stimulus was moving in the same direction as the slow phase of the nystagmus.

Traces three and four were recorded in a similar manner whilst the patient was taking baclofen 10 mg thrice daily. Spontaneous nystagmus in the primary position has been abolished, first degree nystagmus still occurs during saccadic eye movements to right and left but there is no longer any shift of the null position.

Oscillopsia is common in periodic alternating nystagmus.⁶ It is particularly troublesome because, for most of the cycle nystagmus occurs in the primary position. This patient was rendered asymptomatic for most activities whilst taking baclofen because this feature was abolished. Periodic alternating nystagmus is uncommon and easily missed. The present case illustrates that whatever the underlying disorder, it is worthwhile looking specifically for the condition in any patient complaining of oscillopsia as it appears to be one of the few such eye movement disorders for which effective treatment is available.

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